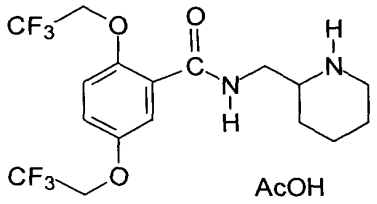
TITLE OF INVENTION

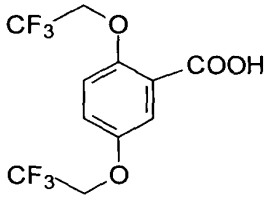
[0001] A novel process for the preparation of Flecainide, its pharmaceutically acceptable salts and important intermediates thereof.

BACKGROUND

[0002] Flecainide acetate, 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide acetate (I), is a drug for the treatment of arrhythmia. It and its neutral base are described in US patent No. 3,900,481.



(I)



(II)

[0003] A key intermediate for the synthesis of Flecainide and its pharmaceutically acceptable salts is 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (II). One prior method for the preparation of this intermediate, disclosed in British patent No. GB 2045760, is a multistep process which comprises the preparation of 1,4-bis(2,2,2-trifluoroethoxy)benzene from hydroquinone using the very expensive reagent trifluoroethyltriflate ($CF_3CH_2OSO_2CF_3$). 1,4-bis(2,2,2-trifluoroethoxy)benzene is then converted to 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (II) through a multistep process. An alternative method described in the same patent begins from 1,4-dibromobenzene, which is then condensed with more than 8 equivalents of 2,2,2-trifluoroethanol, to furnish the 1,4-bis(2,2,2-trifluoroethoxy)benzene intermediate. 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (II) is also be prepared starting from 1-bromo-4-fluorobenzene (PCT WO 02/066413) or from 2-bromo-5-chlorobenzoic acid (PCT WO 99/02498). All these approaches have limited commercial utility due to the cost of the reagents and the necessity for specialized equipment.

[0004] The method disclosed in British patent No. GB 2045760 for the preparation of the Flecainide base starts from 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid which is converted to its acid chloride and reacts either with 2-(aminomethyl)piperidine to form Flecainide in one step or with 2-(aminomethyl)pyridine, followed by catalytic hydrogenation of the pyridine ring, to form Flecainide base in two steps. The disadvantage of the one step process is that the acid chloride reacts non-selectively with both nitrogen atoms of the 2-(aminomethyl)piperidine, resulting in a mixture of the two acylated isomers.

[0005] Other preparations of Flecainide base are disclosed in WO 99/02498 and US2003/0032835. The process disclosed in WO 99/02498 starts from the cyanomethyl ester of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, which selectively reacts with the primary amino group of 2-(aminomethyl)piperidine to furnish Flecainide. US 2003/032835 discloses a procedure which involves converting 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid to its activated 2,2,2-trifluoroethyl ester which then selectively reacts with the primary amino group of 2-(aminomethyl)piperidine to furnish Flecainide. Although activated esters of this type can be used for the formation of Flecainide, the reagents required to prepare them are expensive on the industrial scale. Moreover, the resulting cyanomethanol and 2,2,2-trifluoroethanol by-products are highly toxic. Esters from less expensive, non-toxic and readily available alcohols are still desired for commercial purposes. Based on the above deficiencies, a new process overcoming these deficiencies was required.

SUMMARY OF THE INVENTION

[0006] It is an object of this invention to provide a novel commercial process for the preparation of Flecainide base, its acetate salt or other pharmaceutically acceptable salts, starting from commercially available and inexpensive halobenzoic acids of formula III, where X^1 is F, Cl, Br, or I, and R^1 is selected from H, alkali metal, or a C_1 to C_9 alkyl group.

[0007] Scheme 1 outlines the method of preparation of Flecainide. The method includes the following advantages:

1) begins from the inexpensive and readily available 2-halobenzoic acid

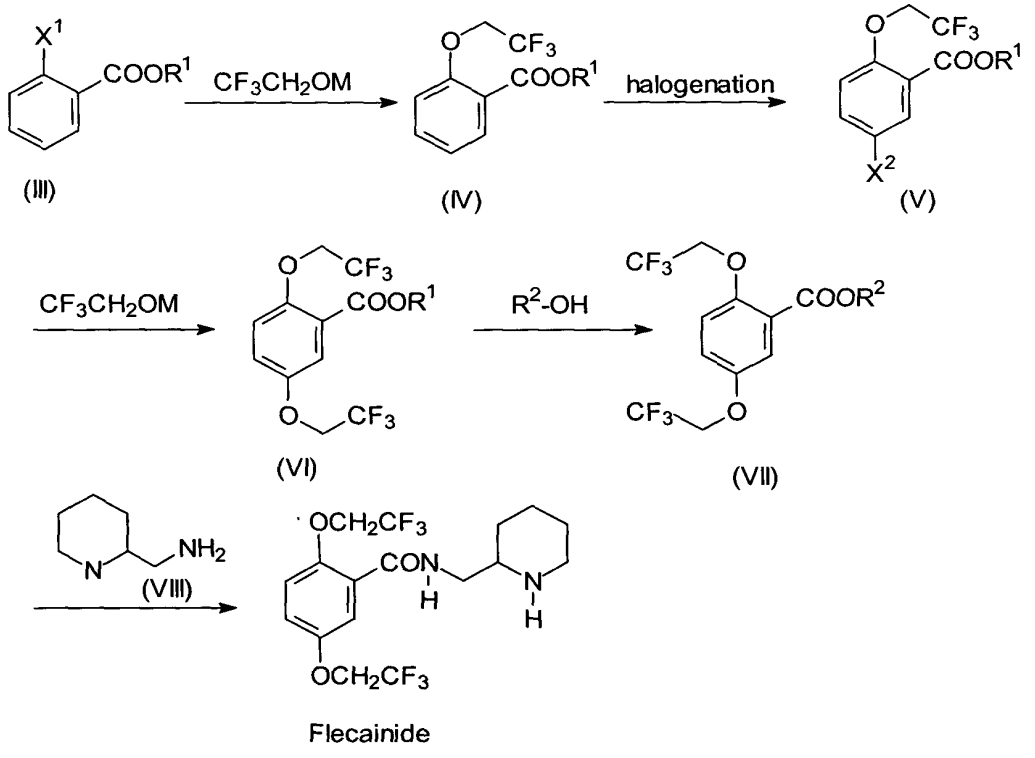
2) high selectivity in the halogenation and amide formation steps

4) high yield

5) low cost solvents used throughout

6) amenable for large scale production and does not require specialized equipment.

Scheme 1



Flecainide

[0008] It is also an object of this invention to provide a process for the preparation of the key intermediate 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid and it derivatives

of the formula **VI** beginning with the inexpensive starting material of the formula III, where X^1 is F, Cl, Br, or I, and R^1 is selected from H, alkali metal, or a C_1 to C_9 alkyl group. Reaction of the starting material of formula III with 2,2,2-trifluoroethanol or any of its suitable derivatives in the presence of a base and a suitable catalyst such as a copper type catalyst provides compounds of the formula IV in high yield (e.g., 80 to 90%). Other suitable catalysts include the palladium and nickel types.

[0009] Compounds of formula IV can be converted to 5-halo substituted compounds of formula V by selective halogenation in the 5-position of the aromatic ring in near quantitative yield. A second coupling between the halogen compound (V) and trifluoroethanol or any of its suitable derivatives in the presence of base and a suitable catalyst such as a copper type catalyst provides compounds of formula VI in high yield, where R^1 is selected from H, alkali metal or a C_1 to C_9 alkyl group.

[0010] It is also an object of this invention to provide a process for the production of Flecainide from 2-(aminomethyl)piperidine and the compounds of the formula VII, where R^2 is selected from C_1 to C_9 alkyl group, aryl groups, succinimidyl and the like, more preferably R^2 is selected methyl, ethyl, benzyl, phenyl, and the like.

[0011] It is yet another object of the present invention to make and use the intermediate 5-bromo-2-(2,2,2-trifluoroethyoxy) benzoic acid to manufacture Flecainide.

[0012] Surprisingly we have discovered that the simple esters of 2,5-bis(2,2,2-trifluoroethoxy)- benzoic acid such as methyl, ethyl and benzyl esters can selectively react with the primary amino group of 2-(aminomethyl)piperidine to produce Flecainide with high yield and high purity. The alcohols used to form those benzoates are inexpensive, readily commercially available and have relatively low toxicity.

DETAILED DESCRIPTION OF THE INVENTION

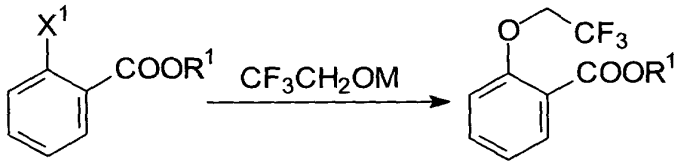
[0013] In one aspect of the present invention, compounds of formula VI are prepared from the compounds of formula III as the starting material.

a) Conversion of 2-halo compounds of formula III to 2-(2,2,2-trifluoroethoxy) substituted compounds of the formula IV (Scheme 2)

[0014] As illustrated in Scheme 2, compounds of formula III are reacted with an alkali or alkaline earth metal 2,2,2-trifluoroethoxide, which can be pre-prepared or generated in situ from 2,2,2-trifluoroethanol and a base, in the presence of a suitable catalyst such as a copper, palladium or nickel containing catalyst in a polar solvent. Compounds of formula III are compounds where X^1 is selected from F, Cl, Br and I and R^1 is selected from H, alkali metals, aryl, and a C_1 to C_9 alkyl group. The alkali or alkaline earth metal ion M can be sodium ion, potassium ion, calcium ion or lithium ion. The preferable solvents are dipolar aprotic solvents, such as N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, dimethyl sulfoxide, methylethylpyridine. The bases used to deprotonate the 2,2,2-trifluoroethanol include sodium, sodium hydride, sodium amide, sodium and potassium alcoholates, lithium hydroxide, sodium hydroxide, potassium hydroxide and calcium hydroxide. Among them, sodium and sodium hydride were used in similar transformations in the prior art, but they react violently with alcohols and water, and generate hydrogen gas, which is a highly flammable and explosive gas. Reagents of this type are therefore unsafe for large-scale production. In the present invention, preferable bases which overcome the deficiencies of the prior art include sodium methoxide, sodium isopropoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, and the like. The most preferable base is potassium *tert*-butoxide. Compared to sodium metal and sodium hydride, they are much safer for handling in large scale. They are also readily commercially available, and produce the product in high yield and purity. Such suitable catalysts for this transformation are preferably copper-containing catalysts that can include cupric chloride, cupric bromide, cupric iodide, cuprous

chloride, cuprous bromide, cuprous iodide, copper (I) oxide, copper (II) oxide, and copper-zinc alloy. The reaction may be performed at temperatures between 0°C to 200°C, preferably between 80°C to 120°C.

Scheme 2



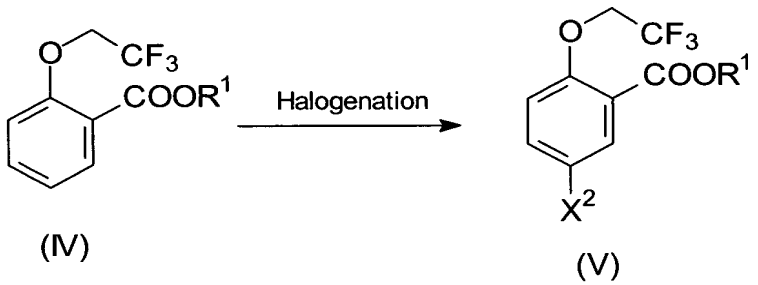
(III) (IV)

b) Conversion of compounds of formula IV to 5-halo substituted compounds of the formula V (Scheme 3)

[0015] The compounds of formula IV are halogenated selectively at the 5-position to provide compounds of formula V, where X^2 is selected from Cl, Br or I. This reaction may be performed in the presence of a Lewis acid catalyst. The halogenation reagent may be any of the normally anticipated reagents used for halogenation reactions such as chlorine, N-bromosuccinimide, bromine, N-iodosuccinimide, or iodine. Examples of preferable Lewis acids include, but are not limited to, zinc chloride, zinc bromide, iron, iron chloride, aluminum chloride, aluminum bromide, and boron trifluoride etherate. More preferably, this transformation is performed with bromine and a Lewis acid such as aluminum chloride or iron chloride, due to the fact that they afford high selectivity and resulting in high yield. They are also readily available on an industrial scale and are relatively inexpensive. The solvents may be nonpolar hydrocarbon based, for instance, hexane, heptane, octane, cyclohexane, or polar solvents, for instance, N,N-dimethylformamide, dichloromethane, 1,2-dichloroethane, dimethyl sulfoxide, acetonitrile, tetrahydrofuran, acetic acid and ethyl acetate. Preferable solvents are

dichloromethane and 1,2-dichloroethane. The reaction is carried out at temperature between -20°C to 80°C, preferably between 0°C to 20°C.

Scheme 3



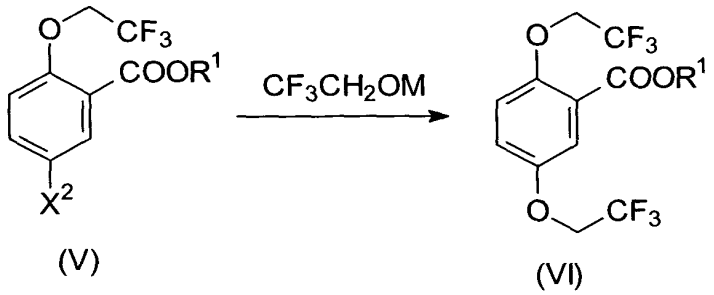
(IV) (V)

c) Conversion of 5-halo substituted compounds of formula V to compounds of formula VI (Scheme 4)

[0016] Compounds of formula V can be converted to compounds of formula VI under similar conditions as described in step a) above, where reaction of the substrate with 2,2,2-trifluoroethanol or any of its suitable derivatives in the presence of a strong base and a suitable catalyst such as a copper, palladium or nickel containing catalyst in an aprotic solvent occurs. The alkali or alkaline earth metal ion M can be sodium ion, potassium ion, calcium ion or lithium ion. The preferable solvents are dipolar aprotic solvents, such as N,N-dimethylformamide, 1-methyl-2-pyrrolidinone, dimethyl sulfoxide. The bases used to deprotonate the 2,2,2-trifluoroethanol include sodium, sodium hydride, sodium amide, sodium and potassium alcoholates, lithium hydroxide, sodium hydroxide, potassium hydroxide and calcium hydroxide. Among them, sodium and sodium hydride were used for similar transformations in the prior art, but they react violently with alcohols and water, generating hydrogen gas, which is a highly flammable and explosive gas, thereby making these bases unsuitable for large-scale production. In the present invention, the preferable bases include sodium methoxide, sodium isopropoxide, sodium *tert*-butoxide, potassium *tert*-butoxide and the like. Compared to sodium metal and sodium hydride, they are much safer for handling on industrial scale.

They are also readily commercially available, as well as produce the product in high yield and purity. The preferable catalysts are copper-containing catalysts that include cupric chloride, cupric bromide, cupric iodide, cuprous chloride, cuprous bromide, cuprous iodide, copper (I) oxide, copper (II) oxide, and copper-zinc alloy. The reaction may be performed at temperatures between 0°C to 200°C, preferably between 80°C to 120°C.

Scheme 4

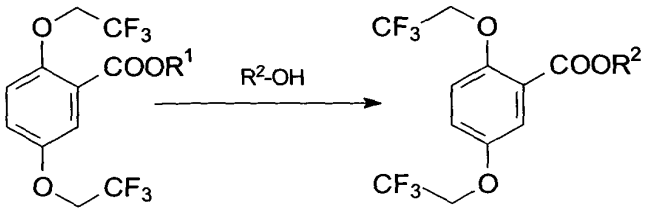


(V) (VI)

Conversion of compounds of the formula VI to compound of formula VII (Scheme 5)

[0017] Compounds of formula VI may be converted to Flecainide directly by selective amidation of 2-(aminomethyl)piperidine. Compounds of formula VI can also be converted to a new ester of formula VII by reaction with a hydroxyl compound R^2-OH. The preferable methods of this transformation include conventional esterification, transesterification, and activation of the acid, for instance by conversion to its acid chloride followed by reacting with a hydroxyl compound R^2OH. These transformations are well known to those skilled in the art. The R^2 is selected from C_1 to C_9 alkyl group, aryl groups, succinimidyl and the like. More preferably R^2 is selected from methyl, ethyl, benzyl, phenyl, and the like because the alcohols used to prepare these esters are inexpensive, readily commercially available and are relatively non-toxic. The simple benzoates selectively react with the primary amino group of 2-(aminomethyl)piperidine (VIII) to form Flecainide in high yield and purity under the conditions of the present invention.

Scheme 5



(VI) (VII)

[0018] The compounds of formula VI or VII are converted to Flecainide, as Flecainide base or pharmaceutically acceptable salts thereof, by selectively coupling at the primary amino group of 2-(aminomethyl)piperidine. The reaction is mainly dependant upon the solvents, temperature, concentration, and the ratio of the substrates.

[0019] The reaction occurs in the absence or in the presence of solvent. The solvents may be aromatic, aliphatic, or cycloaliphatic solvents, from five to ten carbons or ethers from four to ten carbons, for example, hexane, heptane, cyclohexane, toluene, xylenes, diethyleneglycol dimethyl ether (diglyme), 1,2-dimethoxyethane (glyme), acetonitrile, methylene chloride, or tetrahydrofuran, more preferably toluene and xylenes. The reaction temperature range is between 0°C to 150°C, more preferably is between 50°C to 120°C. The molar ratio between the benzoate and the piperidine is 1:1 to 1:2, most preferably is 1:1 to 1:1.5.

[0020] The Flecainide base obtained by crystallization from the reaction base is easily converted into pharmaceutically acceptable salts via salt-forming reactions well known in the art.

[0021] The following non-limiting examples illustrate the process in producing Flecainide base or its pharmaceutically acceptable salts by the process of the present invention.

Example 1

[0022] Preparation of 2-(2,2,2-trifluoroethoxy)benzoic acid

[0023] To a solution of 2,2,2-trifluoroethanol (40.0 g) and DMF (100 ml) was added sodium *tert*-butoxide (23.0 g) at 0°C. The solution was stirred at 20 to 25°C for 1 hour at which point 2-chlorobenzoic acid (25.0 g) was added followed by cupric bromide (2.0 g). The mixture was stirred at 120°C for 5 hours, cooled to 10°C, and water (30 ml) was added followed by 20% HCl solution (90 ml). The solution was extracted with dichloromethane (3 X 50 ml). The combined organic layers were washed with water (3 X 50 ml) and the volume was concentrated to 90 ml. Hexane (150 ml) was added to the residues, and the mixture was concentrated to volume of 120 ml and a further portion of hexane (30ml) was added. The mixture was heated at 50°C for 30 minutes and then stirred at room temperature for 1 hour. The solids were filtered to yield the crude product. This material was dissolved in ethyl acetate (50 ml), charcoal (1.7 g) was added and the mixture was stirred at room temperature a further 2 hours. The solution was filtered through Celite™ and crystallized from ethyl acetate/hexane to yield the pure product (30.9 g, yield 88.0%) as a white solid, m.p. 85-86°C.

Example 2

[0024] Preparation of 5-bromo-2-(2,2,2-trifluoroethoxy)benzoic acid

[0025] To a solution of 2-(2,2,2-trifluoroethoxy)benzoic acid (22 g) in methylene chloride (100 ml), was added $AlCl_3$ (13.3 g) at 0°C followed by bromine (16.0 g, 0.1 mol). The reaction mixture was stirred at 0°C for 1 hour and then at reflux for 2 hours. The solids were filtered and water (50 ml) and ethyl acetate (50 ml) were added to the filtrate. The aqueous layer was separated and extracted with ethyl acetate (2 X 60 ml) and the combined organic layers were washed with water (2 X 60 ml). The organic layer was concentrated under vacuum to dryness and hexane (100

ml) was added and the resulting suspension was stirred at 20 to 25°C for 1 hour. The mixture was filtered and the cake was rinsed with heptanes (2 X 20 ml). The damp solids were dried in vacuum at 45°C for 5-6 hours to give a white solid (28.3 g, yield 94.6%), m.p. 126-128°C.

Example 3

[0026] Preparation of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid.

[0027] To a solution of 2,2,2-trifluoroethanol (14.7 g) and DMF (125 ml) was added sodium *tert*-butoxide (12.8 g) at 0°C. The solution was stirred at 20 to 25°C for 1 hour at which point 5-bromo-2-(2,2,2-trifluoroethoxy)benzoic acid (20 g) was added followed by cupric bromide (2.0 g). The mixture was stirred at 100°C for 10 hours, cooled to 10°C, and water (30 ml) was added followed by 20% HCl solution (90 ml). The solution was extracted with dichloromethane (3 x 80 ml), and the combined organic layers were washed with water (3 X 60 ml). The solution was concentrated to one-third of the original volume and hexane (200 ml) was added. The resulting suspension was stirred at room temperature for 2 hours, filtered and the damp cake was rinsed with hexane (2 X 40 ml). The damp cake was dried in vacuo at 40°C for 5 hours to give the product as a white solid (16.02 g, yield 75.3%).

Example 4

[0028] Preparation of methyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate

[0029] A solution of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid (20g) and thionyl chloride (15.0 g) in methanol (100 ml) was stirred at 80°C for 2 hours. The solvents were evaporated under vacuum to give an oil residue. Toluene (100 ml) was added to the residue and the solution was washed with saturated $NaHCO_3$ (30 ml) solution followed by water (3 X 30 ml). The organic layer was concentrated under reduced pressure to give the product as a white solid (20.5 g, yield 98.0 %).

Example 5

[0030] Preparation of Flecainide

[0031] A mixture of methyl 2,5-bis(2,2,2-trifluoroethoxy)benzoate (1.5 g), 2-(aminomethyl)piperidine (0.62 g) in toluene (3 ml) was stirred at reflux for 10 hours. After cooling to room temperature, water (10 ml) was added and two layers solution were separated. The aqueous layer was extracted with toluene (2 X 10 ml) and the combined organic layers were washed with water (3 x 10 ml). The organic layer was concentrated under reduced pressure to give Flecainide free base as a white solid (1.63 g, 85%).

Example 6

[0032] Preparation of Flecainide acetate

[0033] To a solution of Flecainide free base (1.5 g) in isopropanol (7.5 ml) was added glacial acetic acid (0.3 g) and the solution was stirred under reflux for 2 hours. The solution was cooled to room temperature and hexane (15 ml) was added and solids began to precipitate. The resulting suspension was stirred at 20-25°C for 2 hours and the solids were filtered and then rinsed with hexane (2 X 10 ml). The damp cake was dried in vacuum for 4 hours to give Flecainide acetate as a white solid (1.54 g, Yield 89%).